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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/588,778	12/03/2007	Hiide Yoshino	2006_1312A	4646

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EXAMINER	
SZNAIDMAN, MARCOS L	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
05/17/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/588,778	YOSHINO ET AL.	
	Examiner	Art Unit	
	MARCOS SZNAIDMAN	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 January 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to applicant's reply filed on January 21, 2010.

Receipt of Declarations under 37 CFR 1.132 is acknowledged.

Status of Claims

Amendment of claims 1-2, 8-9 and 13-16 and cancellation of claims 17-32 is acknowledged.

Claims 1-16 are currently pending and are the subject of this office action.

Claims 1-16 are presently under examination.

In the reply of April 29, 2009, Applicant elected without traverse the species: 3-methyl-1-phenyl-2-pyrazoline-5-on (edaravone) as the compound of formula I. Due to applicant's arguments filed on January 21, 2010, the above species is free of prior art, so the examination was expanded to the remaining species encompassed by formula I, which are also free of prior art.

Priority

The present application is a 371 of PCT/JP05/001932 filed on 02/09/05, and claims priority to foreign application: JAPAN 2004-032420 filed on 02/09/2004 and JAPAN 2004-032421 filed on 02/09/2004.

Should applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d) prior to declaration of an interference, a certified English translation of the

foreign application must be submitted in reply to this action. 37 CFR 41.154(b) and 41.202(e).

Failure to provide a certified translation may result in no benefit being accorded for the non-English application.

Rejections and/or Objections and Response to Arguments

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated (Maintained Rejections and/or Objections) or newly applied (New Rejections and/or Objections, Necessitated by Amendment and/or New Rejections and/or Objections not Necessitated by Amendment). They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112 (New Rejection not Necessitated by Amendment)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of ALS (Amyotrophic Lateral Sclerosis) with Ederavone, it does not enable for the treatment of ALS with other compounds encompassed by formula I. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the

invention commensurate in scope with these claims. This is a scope of enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996). As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1- the quantity of experimentation necessary,

2- the amount of direction or guidance provided,

3- the presence or absence of working examples,

4- the nature of the invention,

5- the state of the prior art,

6- the relative skill of those in the art,

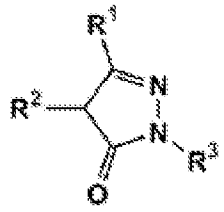
7- the predictability of the art, and

8- the breadth of the claims

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention

Claims 1-16 recite a method of treating ALS or symptoms caused by ALS and/or suppressing the progression thereof, which comprises administering to a patient in need thereof as an active ingredient a pyrazolone compound represented by the following formula I:



(I)

under the condition that a drug holiday period of 1 day or more is provided once, twice or more during the period for treating the disease or suppressing the progression of the disease.

2. The relative skill of those in the art

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

3. The state and predictability of the art

As illustrative of the state of the art of treating ALS in general, the Examiner refers to Jackson et. al. (Expert Opinion on Investigational drugs (2002) 11:1343-1364).

Jackson teaches that ALS is a progressive neurodegenerative disease characterized by the selective dead of motor neurons. The mechanisms and process responsible for the selective loss of motor neurons are still unknown. Unfortunately the majority of therapeutics found to be efficacious in the animal and cell culture models have failed in human trials. Riluzone is still the only proven therapy in humans, shown to extend survival of ALS patients by 3 months, but it has no effect on muscle strength (see abstract).

Table 1 on page 1349 shows most of the clinical trials that have been performed in the past, showing that the majority resulted in negative results.

Regarding the treatment of ALS with compounds of formula I, the Examiner refers to Ikeda (US 6,933,310, cited in prior office action).

Ikeda teaches a method of treating ALS comprising the administration of 3-methyl-1-phenyl-2-pirazoline-5-on (edaravone, R1 = Methyl, R2 = Hydrogen and R3 = Phenyl) (see for example claims 1-5). Ikeda further teaches that the route of administration of the medicament is not particularly limited (see column 5, lines 10-14) and that the medicament can be administered directly to the patient preferably in the form of a pharmaceutical composition (see column 5, lines 15-21). Ikeda only provides animal data. Ikeda does not teach the treatment of ALS with any other close related compound.

These articles demonstrate that the art of treating ALS in general and with compounds of formula I in particular is highly unpredictable.

4. The breadth of the claims

Claim 1 is very broad in terms of the compounds claimed.

5. The amount of direction or guidance provided and the presence or absence of working examples

MPEP 2164.03 states: "The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required. A single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements. *In re Vickers*, 141 F.2d 522, 526-27, 61 USPQ 122, 127 (CCPA 1944); *In re Cook*, 439 F.2d 730, 734, 169 USPQ 298, 301 (CCPA 1971). However, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed.

Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work".

Applicant shows the effectivness of treating ALS in animal models with Ederavone (R1 = Methyl, R2 = Hydrogen and R3 = Phenyl) (see 1.132 declaration). However, Applicant did not provide a reasonable representative set of compounds of formula I to be effective against ALS, as such, and due to the diverse set of compounds encompassed by Formula I, there is no correlation between the treatment of ALS with Edaravone and the remaining compounds of formula I.

As such, if there is no correlation, then the examples do not constitute working examples. While it is understood that the absence of working examples should never be the sole reason for rejecting a claims as being broader than an enabling disclosure, the criticality of working examples in an unpredictable art, such as the treatment of ALS with compounds of Formula I, is required for practice of the claimed invention.

6. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed in section 3) and in the absence of experimental evidence commensurate in scope with the claims (as discussed in section 5), the skilled artisan would not accept that compounds of formula I, except for Edaravone, will effectively treat ALS.

Accordingly, the inventions of claims 1-16 do not comply with the scope of enablement requirement of 35 U.S.C 112, first paragraph, since to practice the claimed

invention a person of ordinary skill in the art would have to engage in undue experimentation with no reasonable expectation of success.

Withdrawn Rejections and/or Objections

Claims rejected under 35 USC 112, first paragraph (written description).

Due to applicant's amendments, the written description rejection is now moot.

Rejection under 35 USC 112, first paragraph (written description) is withdrawn.

Claims rejected under 35 USC 112, second paragraph.

Due to applicant's cancellation of claims 17-32, the 35 USC 112, second paragraph rejection is now moot.

Rejection under 35 USC 112, second paragraph is withdrawn.

Claims rejected under 35 USC 103(a)

Applicant was able to demonstrate unexpected results for the treatment of ALS with Ederavone under the specific dosage regime claimed; which would not have been obvious based on the prior art, as such the 103(a) rejection was overcome.

Rejection under 35 USC 103 is withdrawn.

Conclusion

No claims are allowed.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCOS SZNAIDMAN whose telephone number is (571)270-3498. The examiner can normally be reached on Monday through Thursday 8 AM to 6 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MARCOS SZNAIDMAN/
Examiner, Art Unit 1612
March 31, 2010